REMARKS

Claim Amendments

Claims 18 and 20 have been newly cancelled and claims 15, 16, 21 and 24 have been amended as follows:

- Independent claims 15 and 16 have been amended to remove the recitation of "excluding AZD2171 maleate salt," and to be more specifically directed toward the treatment of a solid tumour cancer. Support for these claims as amended is found in the specification, *inter alia*, at page 6, lines 1-5 (claim 15) and at page 7, lines 16-22 (claim 16). Dependant claim 20 has been cancelled as now being redundant, in that its further limitation has been incorporated into independent claims 15 and 16.
- The dependencies of claims 21 and 24 have been amended to remove reference to newly-cancelled claim 18.

The above amendments are being made to encompass all salt forms in the same claim set and to adjust the dependencies accordingly, without deleting any salt form from the scope of the claims as a whole. It should be clear from the above that no new matter has been added by the above amendments, and entry thereof is believed to be in order and is respectfully requested. Following entry of the above amendment claims 15-17, 21 and 24 are pending in this application.

Priority

Under the heading "priority" the Examiner states that the "earliest effective US filing date afforded the instantly claimed invention is 03/22/2005, the filing date of PCT/GB05/01079." Actually the PCT application of which the present application is the US National Stage is PCT/GB05/01080, which was also filed on 03/22/2005. However, while it is correct to say that the earliest effective US filing date afforded the instantly claimed invention is 03/22/2005, the actual "*priority*" that has been claimed, and to which the presently claimed invention is entitled, is GB application 0406446.5 filed March 23, 2004.

Double Patenting

Claims 15-21 and 24 are *provisionally* rejected on the ground of nonstatutory obviousness-type double patenting "as being unpatentable over claims 1-6 of copending

Application No. 10/563,439; 10/563,440; 10/594,233; 10/594,234; 11/663,912 in view of Lee (US Pub No. 2002/0002162; Pub. Date Jan. 3, 2002)." (Action at page 3). The Examiner's attention is called to the fact that Application No. 10/594,233 is the *present application*, which it is presumed the Examiner did not intend to cite. Additionally, the Examiner's attention is called to the fact that 10/563,440 is listed as "abandoned" in PAIR, with no pending continuing application and 11/663,912 is listed as "abandoned" in PAIR, with a pending continuing application 12/408,833 filed on March 23, 2009. Otherwise, these applications all remain pending with no claim allowed. Therefore this obviousness-type double patenting rejection remains provisional.

While Applicant does not agree with the Examiner's argument of obviousness-type double patenting, in particular with respect to the application of the Lee reference to this rejection (for reasons discussed below), Applicant need not, and in fact cannot respond to this ground for rejection unless and until claims are allowed in one or more of the reference applications before allowance of the present application.

Claim Rejections - 35 USC § 103

Claims 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee, US Pub No. 2002/0002162 (hereinafter "**Lee '162**") in view of Hilberg *et al.* WO/2004/096224 (hereinafter "**Hilberg '224)**. This ground for rejection is respectfully traversed.

First, the Examiner has made a note after the citation of Hilberg '224 that reads "Prior.date 02/29/2003", and the undersigned is unable to figure out what this note is intended to refer to. The earliest of the three different "priority dates" claimed in Hilberg '224 is April 29, 2003 (not February), and this clearly is not the date on which this reference is *effective as prior art* in the United States. In fact, the *earliest* date on which Hilberg '224 is *effective as prior art* in the United States is its International Filing Date of April 24, 2004. There is no way that this document can be considered *effective as prior art* as of any of its European priority dates.

As noted above under ***Priority***, the present application has claimed and is entitled to priority as of the filing date of its priority application GB application 0406446.5 filed March 23, 2004, which was filed before the earliest *effective prior art date* of Hilberg '224 of April 24, 2004.

It seems that perhaps the Examiner is confusing *priority dates* with *prior art effective dates*. Simply put, a reference document is prior art to an application if the reference is *effective as prior art* on a date that is earlier than the *priority date* to which the application is entitled. Thus again, because Hilberg '224 has an *earliest effective prior art* date of April 24, 2004, which is after the *priority* date accorded the present application, Hilberg '224 is not prior art to the present application.

Therefore, this ground for rejection based on Lee '162 in view of Hilberg '224 must be withdrawn.

Moreover, it is respectfully submitted that the Examiner has mischaracterized what Lee '162 "teach" when asserting in the Action:

> Lee '162 , teaches therapies for treatment of cancer , that further, teach a synergistic method for the treatment of cancer in a mammalian specie[0002,0011] which comprises a vascular endothelial growth factor receptor tyrosine kinase inhibitor, ZD6474 [0082], in conjunction with 5-Fluorouracil [0072, Table 1] and CPT-11 [0074, Table 1] for the treatment of breast, pancreas, bladder colon lung, skin colorectal, non-small cell lung cancer and mesothelioma.[0059-0067].

(Action at pages 5-6; emphasis added).

The actual "teaching" of Lee '162, under any reasonable construction of this reference, and as specifically stated in paragraph [0011], which the Examiner is presumably paraphrasing:

> The present invention provides a synergistic method for the treatment of cancer which comprises administering to a mammalian specie in need thereof a synergistically, therapeutically effective amount of: (1) at least one agent selected from the group consisting of anti-proliferative cytotoxic agents and anti-proliferative cytostatic agents, and (2) a compound of formula I ...

(Lee '162 [0011]); emphasis added). In particular:

- Lee '162 does not *teach*, no less even suggest, synergism with any combination *except with Bristol-Myers' proprietary formula I;*[1]
- Lee '162 does not *teach*, no less suggest, "a vascular endothelial growth factor receptor tyrosine kinase inhibitor, ZD6474 [0082], in conjunction with 5-Fluorouracil [0072, Table 1] and CPT-11 [0074, Table 1]" as the Examiner states; and

[1] Paragraph [0007] of Lee '162 states that US Patent 6,011,029 discloses the formula I compounds. Both Lee '162 and US Patent 6,011,029 state the assignee as Bristol-Myers Squibb.

- Lee '162 certainly does not *teach*, no less suggest, that "synergism" might be obtained by administering a VEGF RTK inhibitor "in conjunction with" 5-Fluorouracil and CPT-11, as the Examiner seems to be suggesting.

Thus, the emphasis throughout Lee '162 is on, first and foremost, the administration of a compound of formula I *in every instance*, in combination with at least one agent selected from the group consisting of antiproliferative cytotoxic agents and antiproliferative cytostatic agents.

It is understood that the Examiner is trying to make a case for other combinations comprising two or more "antiproliferative cytotoxic agents and antiproliferative cytostatic agents" because of the "at least one" recitation, but in every instance there is the mandatory presence of the compound of formula I, and it is *only* the combinations *with formula I* that any synergistic effect is suggested. There is no suggestion anywhere in this reference that *any* benefit (synergistic or not) might be achieved by combining any one of the "antiproliferative cytotoxic agents and antiproliferative cytostatic agents" with any other such agent, except in the presence of a compound of formula I.

Moreover, there is no named or exemplified two-component composition in this reference that includes ZD6474 with the compound of formula I; and there is no three or more component composition that includes ZD6474 or any VEGF RTK inhibitor together with 5-Fluorouracil or CPT-11 (the composition necessarily also including a compound of formula I).

Instead, ZD6474, 5-Fluorouracil and CPT-11 are simply and separately included within the massive list of "anti-proliferative cytotoxic agents and anti-proliferative cytostatic agents" extending over paragraphs [0071] through [0083] from which at least one of such agents is selected for combination with the compound of formula 1. Even under the less rigorous criteria for evaluating obviousness set out by the Supreme Court in *KSR v. Teleflex*, 127 S. Ct. 1727, 82 USPQ2d 1385, there still must be at least some good reason for the skilled person to make the particular selections and the combination thereof to achieve Applicants' invention, without use of hindsight. It is respectfully submitted that there is *no* such reason evidenced by this or any other reference cited by the Examiner. Moreover, it is respectfully submitted that no reasonable, skilled person would waste his or her time consulting an omnibus listing of most every known anti-cancer agent such as this, when looking for effective combination cancer therapies. Therefore, whether or not Hilberg '224 is considered to be prior art to the presently claimed

invention (which it is not), *prima facie* obviousness has not been shown, and this ground for rejection should be withdrawn.

Claims 18, 20-21 and 24 (claims 18 and 20 now being cancelled) are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee '162 in light of Hilberg '224, and "further in view of Lane et al (US Pub.No. 2004/0147541; PCT filed 02/18/2002)" (hereinafter "**Lane '541**"). The above refutations of the rejections based on Lee' 162 and Hilberg '224 apply here as well. Lane '541 is applied here only with respect to the "salt" aspect of previous claim 18, which recited the maleate salt of AZD2171, and claims 18, 21 and 24, which were dependent (in part) on claim 18. Claim 18 and 20 have been cancelled by the above amendments, and the dependency of claims 21 and 24 has been amended to be dependent on claims 15 and 16 only. Therefore, this ground for rejection has been obviated.

Information Disclosure Statement

For completeness of the record, a supplemental Information Disclosure Statement and form PTO-1449 is being submitted herewith on which is listed WO2005/061488, which is the publication of International Patent Application No. PCT/GB2004/005359 that is cited at the bottom of page 3 of the present specification. However, it should be noted that WO2005/061488 is *not* prior art to the present application, in that its earliest *prior art effective date* is the December 18, 2004 filing date of PCT/GB2004/005359. This is subsequent to *priority date* to which the presently claimed invention is entitled, *i.e.,* the March 23, 2004 filing date of GB application 0406446.5. This PCT application entered the US National Stage on June 1, 2006 as US application 10/581,279, which published as US 20070129387A1 on June 7, 2007, and is currently pending with Examiner Tamthom Ngo Truong in GAU 1624, with a predicted first Action in 3 months from the present date.

Technically Related Pending Applications of Applicant's Assignee

The Examiner's attention is called to the following *updated* Table of pending U.S. applications of Applicants' assignee which might be considered technically related, each of which claims a combination of AZD2171 with another therapeutic agent identified under the heading "Combination." The current status of each application as reported in the PAIR database is given in the right-hand column. Each of the published US applications and PCT applications that are in bold on the below table are listed on the form PTO-1449 attached to the Information

Disclosure Statement being submitted herewith, and a copy of each such bold listed published PCT application is provided with the Information Disclosure Statement. All other documents have been previously listed and copies provided in this application.

It is assumed that the Examiner has ready electronic access to each of the pending US applications, but the undersigned will provide a copy of any document from these files if requested by the Examiner.

US Appln. No.	**Date US Filed**	**US Pub. No. Date Published**	**PCT Pub. No. Date Published**	**Combination with**	**Current Status**
10/240,413	October 1, 2002	US 20030144298 July 31, 2003	WO 2001/74360 October 11, 2001	Anti-hypertensive	Assigned to Examiner Charlesworth E. Rae in GAU 1611; Advisory Action Mailed Mailed 04-21-2009.
10/555,389	November 3, 2005	**US 20060223815** October 5, 2006	**WO 2004/098604** November 18, 2004	Anti-angiogenic agent + src inhibitor	Assigned to Examiner Christopher R. Stone in GAU 1614; Response to Non-Final Office Action Entered and Forwarded to Examiner.
10/563,440	January 5, 2006	US 20060160775 July 20, 2006	WO 2005/004871 January 20, 2005	ZD6126	Abandoned
10/563,439	January 5, 2006	US 20060167024 July 27, 2006	WO 2005/004872 January 20, 2005	ZD1839	Assigned to Examiner Benjamin J Packard in GAU 1612; Response to Non-Final Office Action Entered and Forwarded to Examiner.
10/594,235	September 25, 2006	US 20080113039 May 15, 2008	WO 2005/092384 October 6, 2005	Platinum anti-tumor agent, optionally IR	Assigned to Examiner Sharmila Gollamudi Landau in GAU 1611; Response to Non-Final Office Action Entered and Forwarded to Examiner.
10/594,234	September 25, 2006	US 20070135462 June 14, 2007	WO 2005/092385 October 6, 2005	Taxane. optionally IR	Assigned to Examiner Charlesworth E Rae in GAU 1611; Response to Non-Final Office Action Entered and Forwarded to Examiner.
11/663,912	March 27, 2007	US 20080015205 January 17, 2008	WO 2006/035203 April 6, 2006	Imatinib [Gleevec]	Abandoned

US Appln. No.	Date US Filed	US Pub. No. Date Published	PCT Pub. No. Date Published	Combination with	Current Status
11/994,824	January 4, 2008		WO 2007/003933 January 11, 2007	Gemcitabane [Gemzar]	Assigned to GAU 1623, no Examiner assigned; predicted first Action 17 months.
12/158,266	June 19, 2008	**US 20080306094** December 11, 2008	WO 2007/071970 June 28, 2007	pemetrexed	Assigned to Anna Pagonakis in GAU 1614; Non Final Action Mailed 03-25-2009.
12/097,384	June 13, 2008		**WO 2007/068895** June 21, 2007	Angiopoietin-2 antagonist and antagonist of VEGF-A, and/or KDR, and/or Flt1	Assigned to GAU 1644, no Examiner assigned.
12/408,833	March 23, 2009		WO 2006/035203 April 6, 2006	Imatinib [Gleevec]	Application Undergoing Preexam Processing.

The following Table lists a technically related pending U.S. applications of Applicants' assignee that claim a combination of 5-FU and/or CPT-11 with another therapeutic agent identified under the heading "Combination with." The current status of this application as reported in the PAIR database is given in the right-hand column. The published US applications and PCT application were previously cited in this application and a copy of the published PCT application was previously provided.

Again, it is assumed that the Examiner has ready electronic access to this pending US application, but the undersigned will provide a copy of any document from these files if requested by the Examiner.

US Appl	Date US Filed	US Pub #	PCT Pub #	Combination with	Current Status
10/543,106	July 22, 2005	US 20060142316 June 29, 2006	WO 2004/071397 August 26, 2004	ZD6474	Assigned to Examiner Christopher Stone in GAU 1614; Notice of Appeal Filed 01-15-2009.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit

Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
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Date: **April 29, 2009**
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